REMARKS

Claims 21-42 and 44-57 are currently pending in the present application. Applicants wish to thank the Examiner for the in-person interview conducted November 22, 2005. As discussed in the interview, applicants have hereby amended the currently pending claims to include the presence of small soluble particles in the sustained release film coating to distinguish this coating from the enteric coating. Further, applicants have deleted the language "which is customary per se for sustained-release compositions" from claims 21 and 26. Finally, applicants have amended claim 21 to correct the typographical error and to remove the objection to said claim.

Claims 21-42 have been amended and claims 44-57 have been added to place this application in condition for allowance. Specific basis for the newly added claims can be found at page 3, paragraphs 5-7. Neither the amendments to the claims nor the addition of new claims 44-57 introduce new matter within the meaning of 35 U.S.C. §132. Accordingly, entry of the amendments is respectfully requested.

1. Objection to Claim 21

The Official Action states the following as the grounds for rejection:

> Claim 21, line 7 recites the phrase '*bears and enteric coating film*'. The term 'and' should be grammatically corrected to '**an**' instead. Appropriate correction is required.

Applicants thank the Examiner for her comments and suggestions regarding the subject matter of claim 21. As requested by the Examiner, applicants have corrected the

typographical error in the phrase "*bears and enteric coating film*" to "bears an enteric coating film" in claim 21.

Accordingly, applicants respectfully request that the Examiner withdraw this objection.

2. Rejection of Claims 21, 26, and 43 under 35 U.S.C. § 112, 2nd Paragraph

The Official Action states that claims 21, 26, and 43 are rejected for the following reasons:

> Claims 21, 26, and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim subject matter which applicant regards as the invention.
> Claims 21, 26 and 43 are indefinite because the claim limitation 'a coating film which is customary per se for sustained release compositions' is confusing. Applicant's specification defines the coating film to require the presence of embedded soluble particles or that in which salts are contained (pg. 3). It is unclear whether Applicants intend to claim a polymer coating or a polymer coating having the additional ingredients described present. Polymeric coatings are considered to be a film. If Applicants intend to require that the coating film have additional ingredients present (*i.e.* particles, salts), then the term 'customary' should be eliminated and the polymer plus particles or salt claimed. The term 'coating film' is considered to be generic to polymers per se as well as polymers that have particles or salts embedded therein. Clarification is requested.

Applicants thank the Examiner for her comments and suggestions regarding the subject matter of claims 21, 26, and 43. As discussed during the interview of November 22, 2005, applicants have hereby amended the phrase "a coating film which is customary per se for sustained release compositions" to "a sustained release coating film" in claims 21 and 26.

Additionally, claim 43 has been cancelled. Accordingly, the present grounds for the rejection of claims 21, 26, and 43 have been removed.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection to remaining claims 21 and 26.

3. Rejection of Claims 21-43 under 35 U.S.C. §103(a)

The Official Action states the following as the grounds for rejection:

> Claims 21-43 are rejected under 35 U.S.C. §103(a) as being unpatentable over Dietrich *et al.* (WO 97/02020). Dietrich *et al.* teach an oral fixed combination pharmaceutical composition containing pantoprazole in pellet or tablet form, wherein the drug is at least partly in slow release form, and is administered in combination with an antimicrobial active (see Abstract); page 4, lines 15-30). The invention also relates to an oral pharmaceutical composition for treating a disorder caused by Helicobacter comprising pantoprazole in combination with an antimicrobially-active ingredient (pg. 3, lines 1-6). Dietrich *et al.* teach that the compound is pantoprazole, along with its salts and solvates (e.g., hydrates) (pg. 3, 2nd paragraph). According to Dietrich *et al.*, an oral pharmaceutical composition with delayed and controlled release of active ingredients in pellet or tablet form for pantoprazole is provided (pg. 7, 1st paragraph). The invention also provides for an oral pharmaceutical composition in pellet or tablet form for acid-labile irreversible proton pump inhibitors comprising an alkaline pellet or table form for acid-labile irreversible proton pump inhibitors comprising an alkaline pellet or tablet core, at least one release-slowing, release-controlling intermediate layer (for controlled release of the active agent) and an outer enteric layer, which is soluble in the small intestine, wherein the intermediate layer is formed from a water-insoluble film former. The slowing of release can be achieved, for example by a semi-

permeable membrane (pg. 7, lines 18-29). Dietrich *et al.* teach that the pharmaceutical composition can be a combined administration means, being in either *fixed* of free combination administration forms (pg. 4, lines 15-30).

Medicinal dosage forms include, in particular, tablets, coated tablets or pellets, and microtablets in capsules, with the dosage forms designed to achieve and provide for optimal active ingredient profile (pg. 4, line 31-pg. 5, line 3). A typical dosage for pantoprazole can be regarded as a daily does of from about 0.01 to about 20 mg/kg of body weight (pg. 5, last paragraph).

Suitable and preferred tablet disintegrants for use in the manufacture of tablet cores include crosslinked polyvinylpyrrolidone (crosprovidone), crosslinked sodium carboxymethylcellulose and sodium starch glycolate (pg. 8, last paragraph - pg. 9, line 1).

Film-forming polymers include ethylcellulose, polyvinyl acetate, ammonio methacrylate copolymer type A (e.g., Eudragit® RL) and type B (Eudragit® RS), etc. The release rate can be controlled by incorporating water-soluble pore formers, such as PEG, lactose, mannitol, sorbitol, HPMC, etc and also by the thickness of the coating layer applied (pg. 9, lines 2-10).

Suitable enteric coating polymers include methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl methacrylate copolymer (Eudragit® L) or cellulose derivatives such as carboxymethylcellulose (CMEC), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAR), hydroxypropylmethylcellulose phthalate (HP50, HPSS), hydroxypropylmethylcellulose acetate succinate (HPMCAS) or polyvinyl acetate phthalate. Plasticizers (such as propylene glycol), additives and ancillary substances (e.g., buffers, bases, pigments) can also be added (pg. 9, lines 22-32).

Pharmacologically-suitable alkali-metal, alkaline-earth-metal or earth-metal salts of weak acids and the pharmacologically-suitable hydroxides and oxides of alkaline-earth and earth metals are disclosed and include sodium carbonate, for example (page 8, lines 18-26).

Fillers, binders, lubricants, nonstick agents and the like are also disclosed (pg. 8, last paragraph).

The examples at pages 10-14 demonstrate various

> pantoprazole formulations and methods for preparing thereof.
> With regards to the claim limitation 'coating film which is customary per se for sustained release compositions', it is the position of the Examiner that this phrase limitation imparts no unexpected and/or unusual results. The prior art initially recognizes and teaches similar coating films such as those desired by Applicant (*i.e.*, acrylic/methacrylic acid esters) and thus the properties or results imparted by those coating films would also be the same as Applicant's coating film.
> Dietrich *et al.* teach an oral pantoprazole fixed combination composition in suitable forms, such as tablets, coated tablets, pellets and microtablets in capsules. The composition provides delayed and controlled release of the active ingredient. Dietrich *et al.* teach tablet disintegrants, film-forming polymers, enteric coatings and various additives. Therefore, it is the position of the examiner, that given the teachings *et al.*, it would be *prima facie* obvious for one of ordinary skill in the art to use the specific teachings of Dietrich *et al.* who teach a varied release pantoprazole formulation comprising disintegrants, film-forming polymers, enteric coatings, additives and the like to provide a beneficial formulation. The expected result would be an effective formulation in the treatment of various disorders of the stomach.

Applicants respectfully traverse the rejection of presently pending claims 21-42. The reference of record does not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art

at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants thank the Examiner for her suggestion during the interview of November 22, 2005 to provide a distinction between the sustained-release film coating and the enteric coating required by the presently pending claims. Accordingly, applicants have amended claim 21 to recite that "the sustained-release coating film is a water-insoluble and physiologically tolerable plastic membrane having low swelling power in water and in which small soluble particles are embedded", which language was canceled from claim 43 as discussed during the interview.

The specification of the present application provides support for a sustained-release coating with soluble particles embedded therein, such as lactose crystals or salts, such as ammonium salts (page 3, paragraphs 6-7). The application further distinguishes the sustained-release coating from the enteric coating by incorporation of the following references: EP-B-589981 (corresponding English Application US 5,997,903), EP-B1-244 380, EP-B1-589 981, WO-A-9601624, WO-A-9623500, WO-A-

9624338, WO-A-9402140, WO-A-9712580, and WO-A-9800115 (Page 1, last paragraph; Page 2, first paragraph).

In particular, the references provide the following examples for an enteric coating: methacrylic acid/methyl methacrylate copolymer, cellulose derivatives, shellac, and water-based polymer dispersions (US 5,997,903 col. 2, lines 40-41 and Example I; WO-A-9712580 page 14, lines 22-25; WO-A-9624338 page 11, lines 20-24; EP-B1-244 380 page 15, lines 35-38 and page 16, lines 1-6; WO-A-9601624 page 14, lines 20-26). As such, applicants believe that the prior art clearly establishes an enteric coat different from the presently claimed sustained-release coating film, which requires small soluble particles embedded therein.

Accordingly, the recitation of "a water-insoluble and physiologically tolerable plastic membrane having low swelling power in water and in which small soluble particles are embedded" in presently pending claim 21 enables one of ordinary skill in the art to distinguish between the different enteric coating and sustained-release coating present on the two different administration forms required by the presently pending claims.

In contrast, the prior art of record does not disclose two discrete and separate administration forms as required by the presently pending claims. Therefore, as stated in the Examiner Interview Summary of November 22, 2005, the presently pending claims, which describe the active compound in a capsule in two separate dosage forms, separately bearing either an enteric coating or a sustained-release coating, is distinguished over the prior art of record.

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the present rejection of pending claims 21-42.

4. Rejection of Claims 21-43 under 35 U.S.C. §103(a)

The Official Action states that Claims 21-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (US Pat. No. 5,260,069) in view of Dietrich *et al.* (WO 97/02020).

As the basis of this rejection, the Official Action states:

> Claims 21-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (US Pat. No. 5,260,069) in view of Dietrich *et al.* (WO 97/02020).
> Chen teaches a unit dosage form for delivery drugs into the body, wherein a plurality of populations of pellets is provided within a unit dosage form such as a capsule or tablet (see Abstract). The plurality of pellets or particles are completely enclosed within said capsule, each population of pellets constructed to release a drug into said environment of use, whereby all of said pellets are released from said capsule substantially simultaneously, and exposed to the environment when the capsule disintegrates (col. 6, claim 1). Each pellet contains a core including a drug swelling agent (col. 6, claim 1). Additionally, each pellet is coated with a coating membrane containing (a) a water insoluble, permeable polymer and one or both of (b) a diffusion controlling agent, and (c) a dissolution controlling agent (col. 3, lines 10-16). The dosage units are readily adaptable to a variety of timing intervals, different therapeutic agents and combinations of agents (col. 1, lines 63-68).
> Water permeable and insoluble film forming polymer materials for the coating may include cellulose derivatives, acrylic resins, copolymers of acrylic acid and methacrylic acid esters with quaternary ammonium groups and copolymers of acrylic acid and methacrylic acid esters (col. 3, lines 33-38); col. 7, claim 7).
> Water permeable and soluble film forming agents may include enteric polymers, such as cellulose acetate phthalate, cellulose acetate trimellitate; shellac and methacrylic acid copolymers, such as Eudragit and hydroxypropylmethyl cellulose phthalate (col. 3, lines 48-55); col. 7, claim 9).

Swelling agents taught include cross-linked polyvinylpyrrolidone (crospovidone), cross-linked carboxymethylcellulose, sodium starch glycolate and pregelatinized starch (col. 3, lines 43-47).
The unit dosage forms taught by Chen include discrete aggregates of populations of pellets contained in capsules, or compressed into tablets or suppositories with binding agents. The dosage form may be arranged to dissolve promptly in any aqueous medium or to resist dissolution in certain environments such as enteric coated tablets which will not release pellets until they have passed the acid stomach and reached the alkaline intestine (col. 5, lines 23-31).
Chen teaches drugs that include antibiotics, tranquilizers, agents acting on the heart, liver, kidney, central nervous system and muscles, contraceptives, hormonal agents, antineoplastic agents and combinations thereof (col. 5, lines 17-22).
The examples at columns 3-5 demonstrate various formulations of multiparticulate, pulsatile unit dosage forms and methods for manufacture thereof.
Chen teaches that the formulations can be used with a variety of active agents including water-soluble as well as water-insoluble drugs or combinations of drugs (col. 3, lines 31-32); (col. 5, lines 17-22). Chen does not teach the drug to be a benzimidazole. It is deemed obvious to one of ordinary skill in the art to employ any particular active ingredient, based on the intended or desired purpose.
Dietrich et al. (WO 97/02020) teach an oral fixed combination pharmaceutical composition containing pantoprazole in pellet or tablet form, wherein the drug is at least partly in slow release form, and is administered in combination with an antimicrobial active (see Abstract); (page 4, lines 15-30). The oral pharmaceutical composition provides for the delayed and controlled release of active ingredients in pellet or tablet form for pantoprazole (pg. 7, 1st paragraph). The composition in pellet or tablet form for acid-labile irreversible proton pump inhibitors comprises an alkaline pellet or tablet core, at least one release-slowing, release-controlling intermediate layer (for controlled release of the active agent) and an outer enteric layer, which is soluble in the small intestine, wherein the intermediate layer is formed from a water-insoluble film former.
It is the position of the Examiner that one of

> ordinary skill in the art would have been motivated to combine the teachings of Dietrich *et al.* within Chen. Chen teaches a dosage form comprising a capsule containing pellets with varying rates of release of the active ingredient. While Chen does not teach the active ingredient to be a benzimidazole, Dietrich *et al.* teach pantoprazole as the preferred active ingredient to treat disorders of the stomach and teach the pantoprazole in a varied or distinct release oral composition.
> Therefore, it would be prima facie obvious for one of ordinary skill in the art at the time of the invention was made to use the combined teachings of Dietrich et al. within Chen to obtain suitable formulations of a benzimidazole, particularly pantoprazole for treating gastric acid conditions. The expected result would be a highly effective pantoprazole composition, which is beneficial for treating disorders of the stomach, as similarly desired by Applicants.

Applicants respectfully traverse this rejection.

As noted above in Section 3, the arguments of which are hereby incorporated by reference in their entirety, Chen fails to disclose the presently claimed compositions, containing two different administration forms for the claimed specific active compound (namely pyridine-2-ylmethylsulfinyl-1H-benzimidazole), one having an enteric coating film, the other having a specific, different sustained release coating film. Dietrich et al. fails to remedy this deficient teaching in any way. Accordingly, the presently pending claims are distinguished over the prior art of record, as recognized in the Examiner Interview Summary of November 22, 2005.

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the rejection of pending claims 21-42 under 35 U.S.C. §103(a).

CONCLUSION

Based upon the above remarks, the presently claimed subject

matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the outstanding rejections and allow all pending claims 21-42 and 44-57. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

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